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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/697,329	10/27/2000	Eiichi Iishi	1422-449P	8402

7590 05/05/2004

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EXAMINER	
HABTE, KAHSAY	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,329	IISHI ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 7 and 12-17 are pending.

Response to Amendment

2. Applicant's amendment filed 2/09/2004 in response to the previous Office Action (Paper No. 29) is acknowledged. The obviousness rejection of claims 7 and 12-15 has been maintained.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaspersen *et al.* {Journal of Label. comp. and Radiopharm., 27, No. 9, 1055 (1989)} in view of Khankari et al. {Thermochemica Acta 248 (1995) 61-79}. Kaspersen et *al.* teaches the multi-step synthesis of Org-3770 (mirtazapine) on page 1058 (Fig.4). On page 1066, Kaspersen *et al.* teaches the synthesis of mirtazapine and the crystallization of the mirtazapine (compound **1c**) from the crude product using methanol/water solvent mixture to achieve colorless crystals. The only difference between applicant's mirtazapine hydrate and Kaspersen's Org-3770 hydrate is that

Kaspersen's hydrate is ^{13}carbon labeled, but the instantly claimed product requires that the mirtazapine be unlabeled. The structure of Kaspersen's mirtazapine and the structure of applicants unlabeled mirtazapine are extremely closely related. Just as the labeled compound clearly suggests the unlabelled so would the labeled hydrate clearly suggest the unlabelled hydrate. This is particularly true since the labeled compound was prepared in order to study what the known unlabelled compound does in the body. As shown in Khanakari et al., hydration alters pharmaceutically important properties such as solubility and the physical and chemical stability of pharmaceutical solids that contributes in the modification of bioavilability and product performance (see page 64). It is obvious to one skilled in the art to modify the labeled Kaspersen's mirtazapine compound to a hydrated unlabeled mirtazapine compound, since hydration alters the physical chemical or biological performance of a pharmaceutical drug (e.g. bioavailability, solubility, stability) and the fact that hydrates are a conventional form of making a pharmaceutical composition as shown in Khankari et al. (see page 77, last paragraph). Thus, the prior art teaching that mirtazapine forms a hydrate in the labeled form would suggest that mirtazapine forms a hydrate in the unlabelled form, since one expects that labeled and unlabeled to have the same physical properties. One is motivated to prepare this unlabled hydrates because (1) drugs are normally administered in their unlabelled form (which is the form that mirtazapine is commercially available in) and (2) the hydrate is a standard pharmaceutical form as is shown by the secondary reference. Thus, the teaching that mirtazpines (albeit labled) forms a

hydrate would provide the motivation for preparing the unlabeled mirtazapine in a hydrate form for pharmaceutical use.

Response to arguments

Applicants arguments filed 02/09/2004 have been fully considered but they are not persuasive.

Applicants indicate: "The present inventors for the first time found out the hydrates of an unlabeled compound. Moreover, they have for the first time found out anhydrous mirtazapine crystals having low hygroscopic properties and high purity by drying the hydrates of unlabeled compound...they have for the first time found out that the hydrates are important intermediates for preparing anhydrous mirtazapine crystals." The examiner disagrees with applicants, since the hydrate of the labeled compounds could just as well be important intermediates for preparing anyhydrous labeled mirtazapine crystals.

Applicants also argue that Kaspersen's mirtazapine compound is used for metabolic studies in animal and man for the determination of the bioavailability, the compound labeled ^{3}H, ^{14}C, and ^{13}C was needed.....labeled compounds prepared by Kapersen et al. are to be administered a single time for studies. There is no teaching or suggestion that labeled compounds are continuously administered to a patient as a therapeutic substance." The examiner disagrees with applicants. As applicant's argument indicates, it seems that all labeled compounds are unfit for pharmaceutical purposes to treat certain diseases. As far as we know, the labeled and unlabeled

crystal mirtazapine compounds can be administered to the body for treatment purposes. The use of labeled compound in research is in fact based on the assumption that they act the same as non-labeled.

Applicants further argue: "Kaspersen et al. teach the preparation of these labeled compounds for use in metabolism studies. However, to remove the labels of Kaspersen necessarily renders the compounds unsuitable for their intended purpose. As such, there would be no motivation to modify the labeled compounds of Kaspersen et al. to use them in treatment." The examiner disagrees with applicants because the intended purpose for both the labeled and unlabeled mirtazapines are not significantly different one from the other. Note that the labeled compound was prepared in order to study what the known unlabelled compound does in the body. It would have been obvious to one skilled in the art use the unlabeled compounds, since the Kaspersen's labeled mirtazapine are used for metabolic studies.

Applicants also argue "[s]ince the labeled compounds are not used for therapeutic pharmaceuticals, there is no motivation in Kaspersen et al. to produce and ascertain the physical properties of the labeled compound in order to use unlabeled compounds for therapeutic pharmaceuticals." The examiner disagrees with applicants. Applicants are speculating. There is no evidence that Kaspersen used the labeled mirtazapine hydrates because the labeled could not be used for therapeutic purposes. Kaspersen's labeled mirtazapine are used for metabolic studies that will give way for the use of the unlabeled compounds in the treatment.

In addition, the examiner would like to refer to the following review article: {Thermochemica Acta 248 (1995) 61-79} that shows that hydrates form an integral part of many solid dosage forms. Also on page 77, the authors conclude: Hydrates form an integral part of many pharmaceutical dosage forms" that indicate that the hydrates are the preferable way to make pharmaceutical compositions. The authors also conclude: "It is evident that hydration or dehydration of a pharmaceutical solid during formulation development or in a final dosage form may adversely affect the physical, chemical and /or biological performance of a pharmaceutical product." Thus, if dehydration adversely affects the physical and/or biological performance of a pharmaceutical product, a pharmaceutical dosage in a hydrated form would be preferable. Therefore, the argument that Kaspersn et al. does not disclose or suggest that crystals of compound 1C as hydrates is not persuasive, since it is obvious to one skilled that the hydrates are the preferable form or conventional way of making pharmaceutical compositions. The anhydrates of mirtazapine crystals are obvious over the hydrates mirtazapine crystals.

Since the hydrate of the labeled compounds could just as well be important intermediates for preparing anyhydrous labeled mirtazapine crystals and the fact that the hydrates are the conventional way of making pharmaceutical formulation as shown above, the obviousness rejection is proper. Note that obviousness can be for any purpose. Here, since unlabeled mirtazapine is known pharmaceutical, its unlabled hydrate can be obvious for pharmaceutical purposes, even if it is not obvious for metabolic studies.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571) 272-0674. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mark L. Berch
Primary Examiner
Art Unit 1624

KH
May 3, 2004